Advances in Dose Addition for Chemical Mixtures

The EPA Risk Assessment Forum published guidelines in 1986 and supplemental guidance in 2000 on conducting health risk assessments of chemical mixtures including component methods based on dose addition. In 2008, the National Academy of Sciences published a report, *Phthalates and cumulative risk assessment: The tasks ahead,* that, among other conclusions, advocated for EPA to assess groups of chemicals associated with a common adverse outcome or disease rather than its current practice of focusing on a common mode of action when applying dose addition. This white paper examines this issue and others related to EPA's use of dose addition methods for evaluating health risks posed by environmental chemical mixtures.

This report supplements the 1986 and 2000 RAF documents with:

1) a summary of the Agency's experience since 2000 in developing and applying methods based on dose addition;
2) a review of new scientific literature since 2000 that specifically relates to dose addition; and
3) a summary of advances across multiple scientific disciplines regarding their potential to improve our understanding of the health effects of chemical mixtures.

The report contains new material that:

1) identifies additional methods based on dose addition for assessing health risks of chemical mixtures, including "integrated addition" and a "multi-route hazard index";
2) facilitates comparison of available methods by providing discussions in one document of all identified regulatory methods based on dose addition for evaluating mixture risks;
3) includes a new decision diagram that describes a process of choosing amongst component methods (specific dose-additive methods and others such as effect addition);
4) discusses how chemicals with adverse outcome pathways (AOP) or mechanisms that converge might result in dose additivity (See Figure 3-4 in White Paper);
5) discusses how chemicals with different dose-response curve shapes can be evaluated for relative potency and assessed with dose-additive approaches; and, finally,
6) looks ahead to how new approach methodologies (e.g., in vitro cell bioactivity; -omics; structure-activity/read-across) may inform and improve the evaluation of the health effects of mixtures.

Methods based on dose addition continue as the primary mixture risk approaches worldwide for assessing environmental chemical mixtures.

The report has been approved by the RAF Technical Panel. It was reviewed by a set of RAF members selected by the RAF who were not authors of the document and those comments have been addressed [but for one on which there is disagreement].

The Risk Assessment Forum recommends the report proceed to a letter peer review.

References

NRC (National Research Council). (2008). Phthalates and cumulative risk assessment: The tasks ahead. Committee on the Health Risks of Phthalates; Board on Environmental Studies and Toxicology; Division on Earth and Life Studies. Washington, DC: National Academies Press.

U.S. EPA (Environmental Protection Agency). (1986). Guidelines for the health risk assessment of chemical mixtures. (EPA/630/R-98/002). Washington, DC: Risk Assessment Forum. [HYPERLINK "http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=22567"]

U.S. EPA (Environmental Protection Agency). (2000). Supplementary guidance for conducting health risk assessment of chemical mixtures (pp. 209). (EPA/630/R-00/002). Washington, DC: Risk Assessment Forum. [HYPERLINK "http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=4486"]